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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,851	07/21/2006	Silvio Aime	57708/460	9446

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KRAMER LEVIN NAFTALIS & FRANKEL LLP
INTELLECTUAL PROPERTY DEPARTMENT
1177 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

EXAMINER	
RIDER, LANCE W	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
08/31/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

klpatent@kramerlevin.com

Office Action Summary	Application No.	Applicant(s)	
	10/552,851	AIME ET AL.	
	Examiner	Art Unit	
	LANCE RIDER	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-14,16,18,19 and 22-27* is/are pending in the application.

4a) Of the above claim(s) *18,19 and 22-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-14 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

The remarks and amendments filed on June 21st 2010 are acknowledged. Claims 10-16 are amended, claims 1-9, 15, 17, 20-21, and 28 are canceled, claims 18-19 and 22-27 are withdrawn.

Response to arguments

Withdrawn Rejections

Receipt and consideration of Applicants' amended claim set and remarks filed on June 21st 2010 is acknowledged. Rejections and objections not reiterated from previous office actions are hereby withdrawn. The following rejections or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10-13 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balaban, et al., International Patent Application Publication WO 00/66180 and Aime, S., et al., (Magnetic Resonance in Medicine, 2002) and in further view Frullano, L., et al., (Topics in Current Chemistry, 2002).

The rejection is MAINTAINED for the reasons of record set forth in the office action mailed on March 19th 2010 and those stated below.

Applicants argue that Balaban does not teach the use of paramagnetic CEST agents, and Aime does not teach non-covalent adducts.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case Balaban, Aime, anf Frullano teach the use of both polyarginine and [LnDOTP] together as CEST agents and teach that polyarginine and [LnDOTP] form noncovalent adducts with one another.

Applicants argue that Frullano is non-analogous art and relates to the technical field of MRI imaging and not CEST MRI imaging.

In response to applicant's argument that MRI imaging is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, CEST MRI is a specific form of MRI. Being a particular type of MRI does not make CEST MRI a non-analogous art to MRI itself, it is merely a particular type of MRI. Both CEST MRI and MRI are analogous arts and the skilled artisan who performs CEST MRI is the same one who works in the larger field of MRI.

Applicants argue that one would not recognize $[LnDOTP]^{4-}$ as a CEST agent.

As previously stated from the teachings of Balaban, Aime (Magnetic Resonance in Medicine, 2002), and Frullano one skilled in the art at the time of the invention would have immediately recognized $[LnDOTP]^{4-}$ as a CEST agent. Balaban teaches that CEST agents require mobile protons. Aime (Magnetic Resonance in Medicine, 2002) teaches that cyclic macrocycles with functional groups containing mobile protons work effectively in CEST MRI. Frullano teaches that $[LnDOTP]^{4-}$ has functional groups with mobile protons, was already a recognized MRI contrast agent, and shares the same core structure as the CEST agents taught by Aime (JACS Communications, 2002).

Applicants argue that Frullano does not teach that $[LnDOTP]^{4-}$ has functional groups with mobile protons.

As stated previously, Frullano teaches the use of the paramagnetic macrocycle $[LnDOTP]^{4-}$ in MRI. Frullano teaches that this macrocycle is predominantly in the 4-state at physiological pH (pH 7.4) and that the molecule has mobile protons indicated by 4 protonation steps occurring between pH 2 and 10. The protonation steps indicate that the protons on $[LnDOTP]^{4-}$ are mobile and exchange with water.

For these reasons applicant's arguments are not found persuasive.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Balaban, et al., International Patent Application Publication WO 00/66180 and Aime, S., et al., (Magnetic Resonance in Medicine, 2002), and Frullano, L., et al., (Topics in Current Chemistry, 2002) as applied to claims 10-13 and 15-17 above, and further in view of Aime, S., et al., (JACS, 1995).

The rejection is MAINTAINED for the reasons of record set forth in the office action mailed on March 19th 2010 and those stated below.

Applicant argues that Aime does not teach inclusion of macrocyclic [LnDOTP] into macromolecular systems.

In response to this argument, applicant's claims recite that the complexes are compartmentalized in biocompatible systems such as protein cavities, which is not the same as inclusion. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., inclusion) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Frullano also teaches that [LnDOTP] complexes interact with positively charged patches on protein surfaces. Aime (JACS, 1995) teaches covalently or non-covalently binding the macrocycle [LnDOTP] and other lanthanide complexes into macromolecular systems such as polylysine (a positively charged protein like polyarginine), albumin, dextran, micelles, and hemoglobin, reading on compartmentalizing the complex in protein cavities. Amie further teaches that [LnDOTP] binds to the protein hemoglobin similar to DPG, which binds in a cleft of the protein, and is competitive with inositol hexaphosphate, that binds to this same cleft indicating that the [LnDOTP] binds into a cleft, i.e. a protein cavity of hemoglobin and provides a reason for using [LnDOTP] with large molecular complexes. Frullano also recognizes the binding of [LnDOTP] into hemoglobin and cites the Aime reference as well as

teaching encapsulating MRI agents in liposomes. (See page 50, paragraph 4 and page 55, paragraph 1.) Further the Balaban reference teaches delivering the agents in emulsions. (See page 17, lines 32-37.)

For these reasons applicant's arguments are not found persuasive.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 10-17 and 28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6-8, 10, 13, 14, and 18 of copending Application No. 10/502701.

It is noted that applicant has requested that this rejection be held in abeyance.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LANCE RIDER whose telephone number is (571)270-1337. The examiner can normally be reached on M-F 11-12 and 1-4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LANCE RIDER/
Examiner, Art Unit 1618

/Jake M. Vu/
Primary Examiner, Art Unit 1618